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(56) References cited:
FR-A-2 376 158

LIFE SCIENCES, vol. 24, 1979, pages 1467-1470, Pergamon PresS, US; E.A. MOJA et al.: "Reduction of REM sleep by a tryptophan-free amino acid diet"

ACTA VITAMIN ENZYMOL (Milano), vol. 29, 1975, pages 72-78; G.L. GESSA et al.: "Tryptophan-free diet: A new means for rapidly decreasing brain tryptophan content and serotonin synthesis"

(73) Proprietor: **BOEHRINGER BIOCHEMIA ROBIN S.p.A.**
Via S. Uguzzona, 5
I-20126 Milan (IT)

(72) Inventor: **Moja, Egidio Aldo**
P.zza Giulio Cesare, 8
20100 Milan (IT)
Inventor: Gessa, Gianluigi
Vico XII S. Giovanni 18/a
09100 Cagliari (Sardegna) (IT)

(74) Representative: **Dr. Ing. A. Racheli & C.**
Viale San Michele del Carso, 4
I-20144 Milano (IT)

(58) References cited:

PHARMACOLOGICAL RESEARCH COMMUNICATIONS, vol. 16, no. 9, September 1984, pages 909-914, Academic Press, London, GB; E.A. MOJA et al.: "Increase in stage 4 sleep after ingestion of a tryptophan-free diet in humans"

Courier Press, Leamington Spe, England.

EP 0 144 051 B1

(56) References cited:

JOURNAL OF NEUROCHEMISTRY, vol. 22, 1974, pages 869,870, Pergamon Press, GB; G.L. GESSA et al.: "Effect of the oral administration of tryptophan-free amino acid mixtures on serum tryptophan, brain tryptophan and serotonin metabolism"

JOURNAL OF FOOD SCIENCE, vol. 45, no. 2, March/April 1980, pages 331-335, Institute of Food Technologists, Chicago, Illinois, US; N.B. HELBIG et al.: "Debittering of skim milk hydrolysates by adsorption for incorporation into acidic beverages"

Description

The present invention refers to a dietetic supplement based on amino acids, which has an effect on sleep, and to a prepackaged food in which it is contained. Said invention also refers to the method of preparation.

For a better understanding of this invention and its inherent problems, the description of said invention is preceded by some brief remarks on the characteristics of human sleep and some of its regulatory biochemical mechanism.

Nowadeys it is possible to make a polygraphic study of human aleep. This methodology consists in simultaneous study of the electroencephalogram (EEG), the electromyogram (EMG) and the electro-oculogram (EDG), obtained by attaching electrodes to exact points on the head and permits the entire sleep cycle to be differentiated into consecutive stages. Two main periods can be distinguished: "non-REM" sleep (in which the eyes are still or move slowly) and "REM" sleep (in which the eyes move rapidly and dreams occur). The non-REM period of sleep can, in turn, be differentiated into four stages (stage 1, 2, 3 and 4), charecterized by a progressive slowing down of the EEG and increasingly deeper sleep. Stage 4 is the deepest and most restorative. The stages described for an adult human are of somewhat constant average duration with the REM stage taking up 20% of slaep, stages 1 and 2 (light sleep) 55% and stages 3 and 4 (deep sleep) 25%.

Thorough research has been carried out on biochemical mechanisms in the brain, which regulate the alternetion and duration of the individual stages of sleep, and on the effects of chemical compounds on these regulatory machanisms.

In particular, the effect of substances introduced into the orgenism through food has been studied. Thus, for example, some authors (Lacey, J. H. et al. Electroencephl. Clin. Neurophysiol. *44*, 275, 1978) have studied the effect on sleep of specific nutrients, like amino acida, the main aim being to correlate variations in calories introduced in thia way with specific variations in the individual stages of sleep. It ahould be especially noted that non research appears to have been done into the affect on slaep of selective deprivation of a singla amio acid by not including it in the protein subatances administarad, wheraaa it has been discoverad that completely stopping administration of food leeds to an increase in slow sleep (McFedyan U. M. et al.: J. Appl. Physiol., *35*, 391, 1973). The action of serotonin, which is present in the brain of humans and memmals, haa been the object of special study. The human organism is not able to syntheeize thia substence directly, but only by using tryptophan as aubstrate. As is known, the letter is an essantial amino acid preeent in many proteins which are ingested into the humen orgenism in food and small quantitiea of it are found in the brain.

There are two different theories about the role played by serotonin in regulating sleep. According to one (Jouvet M., Science *163*: 32, 1969) a reduction in non-REM sleep ia a consequence of the reduction of levels of serotonin in the brain.

On the contrary, Wyatt and Mendelson (Biol. Psychiatry, 5/33, 1972 and Mendelson et al., Biol. Psychietry *10*: 459, 1972) have demonstrated that drugs able to block synthesis and activity of serotonin, such ae p-chlorophenylalanine and methysergide, reduce REM sleep in humans.

Thus, other researchers heve studied the effects on humen slaep of tryptophen, the biochemicel precursor in the synthesis of serotonin.

H. Hartmann et al. (Psychopharmacology *19*, 114, 1971) report that the administration of tryptophen reduces sleep latency time, whereas Wyatt et al. (Lancet, II, 842, 1970) report that deep sleep ia induced by administration of tryptophan. Then, however, Hartmann and Spinweber (Y. New Mental Diseases 167, 497, 1979) record that such an increase in slow sleep only occurs after ingestion of limited quantities of tryptophan (0.25 g), but not after larger quantities, such as 0.5 and 1 g. It is clear that the results of the above-mentioned experiments do not coincide with one another, neither do they allow definitive concluaions to be drawn about the effects of serotonin and tryptophan on human sleep. In particular, data are lacking about the effects on the nature and duration of sleep of edministering totally tryptophan-free amino acid mixtures.

This is especially important after Gessa et al. (J. Neurochém., *22*, 869, 1974; Biggio et al., Life Sci., *14*: 1321, 1974) have shown that administering of particuler diets of essential amino acids, totally tryptophan-free, to rats reduces the level and activity of serotonin in the brain.

This can be explained by the fact that, as tryptophan is not included in the food, the brain is deprived of this substance, where it acts as a biosynthetic precursor of serotonin. Consequently, the synthesis of serotonin in the brain is reduced.

Subsequently, Moja et al. (Sci., *24*: 1467, 1979) have shown that, following administration of tryptophan-free essential amino acid diets to rats, there was a significant reduction in REM sleep.

On the other hand, Concu et al. (IRCS Medical Science *5*, 520, 1977) report that the administration of a tryptophan-free diet to humens is less effective in reducing a state of anxiety than a diet conteining all amino acids.

Surprisingly and unexpectedly it has now been discovered that the administration to humans of completely tryptophan-free mixtures of amino acids determines a significant increase in the percentage of stage 4 sleep, namely the stage of deepest sleep, which ia especially restorative without significant reduction in light and REM aleep.

Therefore, the aim of this present invention is a dietetic supplement based on amino acids, characterized in that it is entirely tryptophan-free and is formulated, in terms of quality and quantity, in such a way as to act specifically on stage 4 sleep in humans, increasing the percentage of said sleep.

Its composition cannot be compared in any wey with other known formulas which are useful for therapy and contain amino acids, in as much as it is specifically formulated for intervening expressly in human sleep and the fourth stage in particular, of which it increases the percentage.

The dietetic supplement according to this invention should contain at least the following amino acids: L-isoleucine, L-leucine, L-lysine, L-methionine, L-phenylalanine, L-threonine and L-valine.

A preferred mixture has been found which is useful for inducing the beat effects on stage 4 sleep. This mixture of the various above-mentioned amino acids, expressed percentage-wise in grams, i.e. per 100 g of the total amino acid content in the dietetic supplement, corresponds to: L-isoleucine (11.4 g); L-leucine (18 g); L-lysine (13.2 g); L-methionine (18 g); L-phenylalanine (18 g); L-threonine (8.2 g) and L-valine (13.2 g).

Nevertheless, it has been found that a totally satisfactory effect on stage 4 sleep can also be achieved by using mixtures of said amino acids, in which the percentages of one or more of the single amino acids are increased or reducad by 50% compared to the preferred percentages. Therefore, the variability limits of the single amino acids in the mixture lie between 4 and 16% for L-isoleucine, 9 and 27% for L-leucine, L-methionine and L-phenylalanine, 7 and 20% for L-lysine, 4 and 12% for L-threonine and 6 and 19% for L-valine.

The dose to be administered and the number of administrations will vary as a function of the patient's age, state of health, weight and seriousness of the illness. Said dose ie between 6 and 25 g of dietetic supplement, the preferred amount for administration being between 12 and 15 g. Other substances can be edded to the dietetic supplement according to the present invention for improving its organoleptic, dietetic and therapeutic properties, es well as giving it the envisaged form of presentation, provided seid substances are completely tryptophan-free.

Object of the present invention are elso some verients of the above-mentioned formula, which are able to meet particular requirements, such as those of a hypercaloric diet, a normocaloric diet, e hypocaloric diet end e diet which also includes, for example, vitamins, minerals and other non-essential amino acids, es can be seen in the examples given below.

In particular, vitemins which can be included in the formula are, for example, A, C, D and the B-group vitamins; emino acids, for exemple, cystine, arginine and histidine; minerels, espacially those containing phosphorus, iron calcium and potassium, compatible with the use envisaged for the present formula.

As far as regards the method of administering the dietetic supplement according to the present invention, it ahould be kept in mind that food and drink, usually taken during the courae of dey with a normal diet, contain proteins of vegeteble and animal origin, more or less rich in tryptophan. It is therefore obvious that patients suffering from insomnia, who wish to have the full beneficial effect of the dietetic supplement claimed in this patent, especially on the deepest stage 4 of sleep, should prefarably abstain from the food end drink of a normel diet which could aupply even large quantities of tryptophan and thus interfere with the action of the dietetic aupplement cleimed in this patent, by lowering the specific action required.

The optional period of abstinence from food and drink potentially rich in tryptophan veries from subject to aubject aa a functlon of ege, weight and degree of lack of atage 4 aleep.

On the other hand, the perticular mixture formulated for the dietetic aupplement of the present invention in its different proposed versions may be a remedy to a necesaary prolonged abstienca from normal food and drink.

Thua, object of the present invention are also dietetic supplements which provide for the addition to the basic formula of other amino acids, glucides, lipids, vitamins, mineral salts and flavours, so as to provide a particular diet, provided for in the different cases of administration, for example, a normocaloric diet, a hypocaloric diet (for example, a sweetener containing fructose, saccharin or asparteme), a hypercaloric diet (using saccharose as sweetener) or even a diet enriched with vitamins, oligoelements or other dietetic substances.

The substances added may be different solid or liquid vehicles, like water or other diluents, binders, edulcorants and other, provided they are inert with regard to the specific activity envisaged for the final product. Thus, the final product may be, for example, in the form of an aqueous solution, a concentrate for diluting, a powder or granules.

Object of the present invention are also, especially, prepackaged foods for meals, for instance for monocaloric meals, which contain the dietetic supplement claimed in this patent and thereby allow for a tryptophan-free normocaloric diet, as a substitute for the usual diet. Said prepackaged foods are presented in granular form or as a solution for infusion.

The process of preparing the dietetic supplement according to the present invention essentially requires that the final product is guaranteed to be tryptophan-free, in as much as the exogenous presence of said substance, even in small quantities, could—as is already known—reduce the degree of the required effect, i.e. prolonging of stage 4 sleep. As is well-known, tryptophan is found in most animal proteins, for example in milk proteins and vegetable proteins, for example soya, normally used in food products.

Nevertheless, protein hydrolysates from these proteins, like other protein hydrolysates, and the single amino acids, obtained from protein hydrolysates, could be conveniently used in the preparation of the

dietetic supplement, object of the present invention, provided that it is ensured they are totally tryptophan-free.

The process of purifying from tryptophan through chromatographic separation, which could permit separation of tryptophan from the other components in the mixture, is too difficult and costly for an industrial process.

As an alternative to chromatographic purification, recourse can be had to a process of enzymatic removal of tryptophane by treating e protein hydrolysate with a tryptophanase, for example, the tryptophanase obtained from purified culture of Escherichia Coli, as described by R. O. Burns and R. O. Moss (Bioch. Biopys. Acta *65*, 233, 1962).

For this purpose the protein hydrolysate, containing the amino acids to be purified, is subjected to enzymatic treatmant with a purified tryptophanase at e temperature of 20°C for 6 to 12 hours, said treatment being carried out in stainless steel containers. The tryptophanase must be found in the hydrolysate at e ratio of about between 1:1,000 and 1:10,000.

Animal protein, like milk protein, or vegetable protein, like soya protein, can be used for the protein hydrolysate. The mass, originating from the enzymatic action, is completely tryptophan-free after this treatment. Seid mass can be optionally then filtered through diatomite and the protein lysate, obtained in this way, is concentreted and evaporated in a dry vacuum. With this process an amino-acid yield of between 95 and 98% is obtained.

Finally, the absence of tryptophan is checked by subjecting the mixtura obteined in this way to chromatographic analysis, for example, in a Beckmann type amino-ecid analyzer and, if necessary, said mixture is supplemented with the essential emino acids, listed above in tha basic formula, which may be missing from it.

Praliminary purification with tryptophanese, by using the ebove described method, will also ba eppropriate, if single amino acids and/or their mixtures are used, which originate from enrichment or purificetion of protein hydrolysetes.

A preferred veriant for tha preperation of the dietetic supplement, object of the present invention, is the mixing of L-emino acids of synthesis, which ere found on the market in the most pure state, the degree of purity being, in eny caae, ascertained from the chromatographic analysis data.

The amino acids mixing techniques, which provide the dietetic supplement, like thosa for mixing seid dietetic supplement with other optional ingredients which have praviously been checked for absence of tryptophen, ere the usuel onea edopted in pharmaceutical practice, known to the experts in this field. As describad above, the finel product will be provided, for exemple, in single-dose forms of an aqueous solution, a concentrate for diluting, e powder, granules, teblats and effervescent teblets, by using conventional diluents and excipiants, provided they are tryptophen-free.

Convantionel excipienta end diluents are, for example, weter, lactosa, dextrose, saccherose, mennitol, sorbitol, cellulose and its derivatives like for inatance carboxymethyl cellulose, talc, stearic ecid, calcium and magnesium stearete, glycol, starch, alginic acid and alginetes, polysorbates, vegeteble oils end zein.

For practical applictaion, the usefulness and adventages offered by the present invention can ba summerized ea followe:

possibility of increasing the percentage of sleep in staga 4, nemely restoretive sleep, during e normal number of hours of sleep;

possibility of attaining e normal duration of stage 4, nemely restorative sleep, even though reducing the number of houra of sleep, when such a reduction is required for various necessities;

complete etoxicity of the product, which daterminas the required therapeutic effact by inducing e dietetic lack of tryptophen, without at the same time introducing foreign or, at any rate, potentially hermful substances into the orgenism;

possibility of being adapted to the different requirements of individuals.

The following examples illustrate, but ere not binding on the present invention.

Example 1

Twelve healthy volunteers, aged between 18 and 48, were used in the experiment. Each subject was made to sleep in the sleep laboratory, equipped for polygraphic recording, for three consecutive nights. The first night was for adaption. On nights two end three each subject received two different dietetic supplements, defined as tryptophan-free diet and control diet respectively. The tryptophan-free diet wes composed as follows: L-isoleucine (1.4 g), L-leucine (2.2 g), L-lysine (1.6 g), L-methionine (2.2 g), L-phenylalanine (2.2 g), L-threonine (1.0 g), L-valine (1.6 g) and saccharose (10.0 g).

The control diet differed from the former by the addition of 0.5 g of tryptophan.

On each night the subjects received just one of the two dietetic supplements mentioned above and the sequence for administering the two supplements was randomized.

During the ten hours preceding edministration of the dietetic supplement the subjects were only allowed to ingest water.

The polygraphic tracings were analyzed by e researcher who was blind with regard to the diet adopted, according to the internationelly accepted technique (Rechtscheffen A. end Kales A., P.H.S., U.S. Government Printing Office, Weshington D.C., 1968), which provides for subdivision of the sleep period into the previously described stages 1, 2, 3, 4 and REM.

The results for the first three hours of sleep are collected together in the table below, which gives the different sleep parameters relative to the nights with complete diet and tryptophan-free diet respectively.

TABLE

EEG sleep characteristics after e tryptophan-free diet in 12 volunteers. Data for the first three hours of recording.

	Control diet containing tryptophan	Tryptophan-free diet	Significance of difference (°)
Sleep latency	14.0 (±13.9)	14.4 (±14.4)	
Total sleep time (min) (T.S.T.)	155.4 (±28.7)	151.3 (28.2)	
Stage 1 (min)	14.2 (±11.2)	10.0 (±5.1)	
(% T.S.T.)	11.8 (±16.8)	7.0 (±3.8)	
Stage 2 (min)	81.4 (±25.6)	68.0 (±30.9)	
(% T.S.T.)	51.2 (±10.3)	44.4 (±16.4)	
Stege 3 (min)	13.2 (±7.3)	14.3 (±8.3)	
(% T.S.T.)	8.2 (±4.3)	9.8 (±5.3)	
Stage 4 (min)	23.7 (±20.3)	40.8 (±26.4)	p<0.02
(% T.S.T.)	14.9 (±12.2)	28.3 (±17.2)	p<0.01
Stage REM (min)	23.0 (±16.4)	17.2 (±12.6)	
(% T.S.T.)	13.9 (±9.5)	10.1 (±8.3)	
Stage 3 letency (min)	40.5 (±34.7)	26.2 (±15.7)	
Stage 4 latency (min)	53.9 (±38.1)	32.7 (±21.2)	p<0.05
Stage REM latency (min)	88.4 (±43.3)	108.4 (±81.6)	
Waking during sleep (min)	8.8 (±16.6)	9.8 (±15.9)	
(number of times)	2.2 (±2.8)	2.0 (±1.9)	

All values represent mean (±S.D.) (standard deviation)
(°) Statistical method for paired data, two-tailed, 11 degrees of liberty.

The first column in the table gives the parameters studied, namely: sleep latency (difference in minutes between start of recording and the first ten consecutive minutes of sleep), percentage of total sleep time in the different stages (1, 2, 3, 4 and REM), latency of stages 3, 4 and REM and duration and number of wakings during sleep. The data in the column are the averages ± the standard deviation of the twelve volunteers studied, relative to the times when the dietetic supplement containing all the amino acids (including tryptophan) was administered. The third column gives analogous data for the dietetic supplement (tryptophan-free). The fourth column shows the statistical significanca of the differences between the data, that is, the differences between the two data groups (with and without tryptophan) were analysed using Student's "t" method for paired data (a statistical test for comparing averages).

Significance is established at p (probability) <0.05, that is, the probability that the difference obtained is random and less than 1 out of 20.

It appears from the table that administration of a tryptophan-free mixture to humans produces a significnat increase in stage 4 and a non-significant compensatory reduction in light and REM sleep.

Example 2

Under experimental conditions according to the procedure in Example 1 the addition of other amino

acids to the diet, like, for example, glycine or alanine, and the doubling per subject of the amount of tryptophan-free essential amino acids ingested intensify the effect of lack of tryptophan by further increasing the percentage of stage 4 sleep.

Example 3

A formulation of essential amino ecids suitable for increasing percentage wise the duration of stage 4 sleep, in which, according to Example 1, the total content of amino acids of 12.2 g consists of: L-isoleucine (1.4 g); L-leucine (2.2 g); L-lysine (1.6 g); L-methionine (2.2 g); L-threonine (1.0 g) and L-valine (1.6 g).

Example 4

A formulation according to Example 1, consisting of the formulation in Example 3 with the addition of 10 g of seccharose, it supplies a dietetic supplement rich in calories.

Example 5

A hypocaloric dietetic supplement is obtained by adding 1 g of fructose to the formula in Example 3.

Example 6

A dietetic supplement enriched with mineral salts is obtained by supplementing the mixture in Example 3 with 0.25 g of calcium phosphate, 0.100 g of iron sulphate and 0.100 g of potassium chloride.

Example 7

A mixture is prepared enriched with vitamins and amino acids according to the following formula:

L-isoleucine (1.0 g); L-leucine (2.4 g); L-lysine (1.5 g); L-methionine (1.4 g); L-phenylalanine (2.0 g); L-threonine (1.4 g); L-valine (1.5 g); L-cystine (0.2 g); vitamin A 5000 i.U.; vitamin B1 (1.6 mg); vitamin B12 (2.5 mg); vitamin PP (18 mg); vitamin B6 (2.4 mg) and vitamin C (100 mg).

Example 8

A dietetic suppiement enriched with amino acids and mineral salts is obtained with the following formule:

L-isoleucine (2 g); L-leucine (1.8 g); L-lysine (1.3 g); L-methionine (1.76 g); L-methylalanine (2.5 g); L-threonine (1.4 g); L-valine (1.5 g); suitable ealts containing calcium (1 g); phosphorus (0.8 g) end iron (15 mg).

Example 9

A prepeckaged food, which contains the dietetic supplement of the present invention, is prepared by mixing under dry conditions in suitable receivers the amino acids, malt, dextrine, fructose, soye iecithin, hydrogeneted food fats and 50% of seccharose and purified weter until blended.

The blended mixture is then granulated under humid conditions end dried in e fluid bed. The grenulee obtained in this wey are then further screened to the required size end all the other components are added for mixing under dry conditions. The end item in the form of eesily dispersible grenules is then subdivided into single-doses with the following average composition:

L-Leucina	2.2 g	Vitamin B	0.55 mg
L-isoleucine	1.4 g	Vitamin PP	10 mg
L-lysine HCl	2.0 g	Vitamin C	23 mg
L-methionine	2.2 g	Vitamin D_2	164 U.I.
L-threonine	1.0 g	Vitamin E	12 U.I.
L-valine	1.6 g	Folic acid	154 mcg
L-phenylalanine	2.2 g	Pantothenic acid	3.3 mg
Malt dextrine	110.0 g	Calcium	250 mg
Saccharose	40.0 g	Phosphorus	206 mg
Fructose	10.0 g	Iron	7.3 mg
Dextrose	20.0 g	Magnesium	65 mg
Soya lecithin	4.0 g	Copper	0.75 mg
Hydrogenated food fats	12.0 g	Zinc	5.45 mg
Vitamin A	1788 U.I.	Potassium	258 mg
Vitamin B_6	0.75 mg	Iodine	60 mcg
Vitamin B_{12}	1.75 mcg	Manganese	1.2 mg
Vitamin B_2	0.36 mg	Sodium	82 mg
Natural flavours q.b.			

When used it can be diluted in about 300 ml of cold or lukewarm weter, thereby obtaining a food in the form of a liquid (milk-shake). If, on the other hand, 4 g of carrageen ere added to the above-mentioned formula and it is diluted with water, a semisolid food is obtained (pudding).

In both cases the contribution of calories in such e formula corresponds to about 940 Kcal and, therefore, to the amount generally ingested from a normal meel.

Example 10

A dietetic supplement in the form of solutions for infusion (for use in hospitals), which can facilitate induction and prolongation of stage 4 sleep, is presented in two ampoules, containing the mixturas indicated below, corresponding to a preferred formula.

They are provided for simultaneous administration at moment of usa.

- Ampoule A (500 ml)

L-isoleucine	4.500 g
L-leucine	5.500 g
L-lysine HCl	3.800 g
L-mathionine	0.500 g
L-phenylalanine	0.500 g
L-threonine	2.250 g
L-valine	4.200 g
L-arginine	3.000 g
L-histidine	1.200 g
Glycine	4.500 g
L-serine	2.500 g
L-alanine	3.750 g
L-proline	4.000 g
Sodium edetate	0.025 g
Sodium metabisulphate	0.400 g
Hydrochloric acid 37%	2.800 g
Inj. distilled water q.b. at 500 ml	

Ampoule B (500 ml)

Injecteble glucose	253.000 g
Calcium chloride	0.294 g
Magnesium chloride	0.508 g
Sodium chloride	0.584 g
Sodium glycerophosphate	3.060 g
Acetic acid	0.540 g
Sodium hydrate drops	0.280 g
Sodium metabisulphate	0.200 g
Inj. distilled water q.b. at 500 ml	

In prepering the single infusion-type solutions all the components are dissolved in distilled apyrogenic water and tha preparation is brought to the required volume. The solution obtained is filtered through an absolute filter (0.2 µ), bottled and sterilized at 121°C for 20 minutes.

Claims

1. Use of tryptophan-free mixture of amino acids for the preparation of a dietetic supplement having a specific effact on stage 4 sleep in humans, characterized in that said mixture is entirely tryptophen-free and contains at least the following amino acids: L-isoleucine, L-leucine, L-lysine, L-methionine, L-phenylalanine, L-threonine and L-valine.

2. Use of the mixture according to Claim 1 characterized in that each component is included in the following percentage: L-isoleucine (4—16%); L-leucine (9—27%); L-lysine (7—20%); L-methionine (9—27%); L-phenylalanine (9—27%); L-threonine (4—12%) and L-valine (6—19%).

3. Use of the mixture of Claim 1 or 2, characterized in that the optimum composition is L-leucine (18%); L-isoleucine (11.4%); L-lysine (13.2%); L-methionine (18%); L-phenylalanine (18%); L-threonine (8.2%) and L-valine (13.2%).

4. Use of the mixture of any preceding claim, characterized in that the total quantity of the essential amino acids is between 6 g and 25 g in weight.

5. Use of the mixture according to any preceding claim, characterized in that it also contains therapeutically useful components chosen from other amino acids, said substances being able to contribute calories, minerals and vitamins, as well as the inert vehicles required by the chosen forms of presentation.

6. Use of the mixture according to any of the preceding claim, characterized in that it is presented in the form of a powder, granules, a solution, a concentrate for diluting or other form known in this specific field, which is convaniant, and in that it is packaged in a way corresponding to the prechosen form.

7. Use of the mixture according to any of the preceding claims, characterized in that it is the only active component contained in a 12.2 g single-dose package.

8. Use of the mixture according to any preceding cleim, characterized in that it is presented in the form of a prepackaged food, of which it is an ingredient.

9. Use of the mixture according to any preceding claim, characteried in that it is presented in the form of solution for infusion.

Patentansprüche

1. Verwendung einer tryptophanfreien Aminosäuremischung zur Zubereitung eines diätetischen Zusatzes mit einer spezifischen Wirkung auf die Phase 4 des menschlichen Schlefes, dadurch gekennzeichnet, daß die Mischung vollständig tryptophanfrei ist und wenigstens die folgenden Aminosäuren enthält: L-Isoleucin, L-Leucin, L-Lysin, L-Methionin, L-Phenylalanin, L-Threonin und L-Valin.

2. Verwendung der Mischung nach Anspruch 1, dadurch gekennzeichnet, daß jede Ingredienz in folgenden Prozentsätzen enthalten ist: L-Isoleucin (4—16%): L-Leucin (7—27%); L-Lysin (7—20%); L-Methionin (9—27%); L-Phenylalanin (9—27%); L-Threonin (4—12%) und L-Valin (6—19%).

3. Verwendung der Mischung nach Anspruch 1 oder 2, dadurch gekennzeichnet, daß die Optimalkomposition folgende ist: L-Leucin (18%), L-Isoleucin (11,4%), L-Lysin (13,2%), L-Methionin (18%), L-Phenylalanin (18%), L-Threonin (8,2%), und L-Valin (13,2%).

4. Verwendung der Mischung nach einem der vorstehenden Ansprüche, dadurch gekennzeichnet, deß die Gesamtmenge der essentialen Aminosäuren zwischen 6 g und 25 g liegt.

5. Verwendung der Mischung nach einem der vorstehenden Aneprüche, dadurch gekennzeichnet, daß sie außerdem unter anderen Aminosäuren ausgewählte nützliche Ingredienzien enthält, wobei diese Stoffe geeignet sind, Kalorien, Mineralien und Vitaminen, sowie die von den gewählten Herstellungsformen verlangten Inertträger einzuführen.

6. Verwendung der Mischung nach einem der vorstehenden Ansprüche, dadurch gekennzeichnet, daß sie in Form von Pulver, Körner, Lösung, Konzentrat zum Verdünnen der anderer auf diesem spezifischen Gebiet bekannten Art hergestellt wird und daß sie in der der gewählten Form entsprechenden Weise verpackt wird.

7. Verwendung der Mischung nach einem der vorstehenden Ansprüche, dadurch gekennzeichnet, daß sie der einzige Wirkstoff ist, der in Tüten für eine Doses von 12,2 g enthalten ist.

8. Verwendung der Miachung nach einem der vorstehenden Aneprüche, dadurch gekannzeichnet, daß sie in Form eines Nahrungamittels, von dem sie ein Bestandteil ist, in Fertigpackung geliefert wird.

9. Verwendung der Mischung nach einem der vorstehenden Ansprüche, dadurch gekennzeichnet, daß sie in Form einer Infusionslöeung geliefert wird.

Revendications

1. Utilieation d'un mélange d'acides aminés dépourvu de tryptophene pour la préparation d'un aupplément diétetique ayant un effet spécifique sur la phase 4 du aommeil humein, ceractérisé en ce que ledit mélange est tout à fait dépourvu de tryptophane et qu'il comprend au moins les ecides aminéa suivantes: L-iaoleucine, L-leucine, L-lysine, L-méthionine, L-phénilalanine, L-tréonine et L-veline.

2. Utiliaation du mélenge selon le revendication 1, ceractérisé en ce que cheque composant est compris dans le pourcentage suivant: L-isoleucine (4—16%); L-leucine (9—27%); L-lysine (7—20%); L-méthionine (9—27%); L-phénilalanine (9—27%); L-tréonine (4—12%); L-valine (6—19%).

3. Utilizetion du mélange selon la revendication 1 ou 2, caractérisé en ce que le composition optimale est: L-leucine (18%), L-isoleucine (11,4%), L-lysine (13,2%), L-méthionine (18%), L-phénilalenine (18%), L-tréonine (8,2%) et L-valine (13,2%).

4. Utilisation du mélenge aelon n'importe laquelle des revendications précédentes, caractérisé en ce que la quantité totale des ecides aminés essentiels est comprise entre 6 g et 25 g.

5. Utilisetion du mélange selon n'importe laquelle des revendicetions précédentes, caractérisé en ce qu'il contient en outre des composants thérapeutiquement utiles, choisia parmi les acides eminés, lesditee substances pouvant introduire des calories, des minéraux et des vitamines, ainsi que des véhiculas inertes demandés par les formes de présentation choisies.

6. Utilisation du mélange selon n'importe laquelle des revendications précédentes, caractérisé en ce qu'il est présenté sous forme de poudre, de granulés, de solution, de concentré à diluer ou d'une autre forme connue dans ce secteur spécifique, qui soit avantageuse, et en ce qu'il ast conditionné de façon correspondante à la forme choisie.

7. Utilisation du mélange selon n'importe laquelle des revendications précédentes, caractérisé en ce qu'il eet le seul composant actif, contenu en sachets monodose de 12,2 g.

8. Utilisation du mélange eelon n'importe laquelle des revendications précédentes, caractérisé en ce qu'il se présente sous forme d'aliment préconditionné, dont il est un ingrédient.

9. Utilisation du mélange selon n'importe laquelle des revendications précédentes, caractérisè en ce qu'il se présente sous forme de solution pour infusion.